GENERIC PHARMACEUTICAL INDUSTRY ASSOCIATION

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Alice E. Till, Ph.D.
President

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August 26, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Re: Draft Guidance for Industry on Changes to an Approved NDA or ANDA [Docket No. 99D-0529]

Sir/Madam:

On behalf of the Science Committee of the Generic Pharmaceutical Industry Association (GPIA), I am submitting comments on "Draft Guidance for Industry on Changes to an Approved NDA or ANDA", FR 64 (123), 34660, June 28, 1999.

GPIA is comprised of the manufacturers and distributors of generic medicines (as well as the providers of technical services and goods to these firms). Many of our members will be directly impacted by implementation of the subject draft guidance.

We would appreciate your consideration of the following comments as you finalize the guidance.

Lines 160 - 162 Equivalence: Only when redocumentation of *in-vivo* bioequivalence is required should the pre-change material selected for comparison be the reference-listed drug. In all other cases, the appropriate comparisons should be between pre-and post-change material as indicated on lines 157 – 159. Therefore, the term "*in-vivo*" should be inserted before "bioequivalence" on line 160.

Lines 174 - 176 Adverse Effect: The language here seems to be equating or correlating "adverse effect" on identity, strength, quality, purity, or potency with a potential clinical "adverse effect (or event)". We recommend deleting or changing the example in this section. It should in no way imply that a new degradant *will* adversely affect the safety profile of a drug if it adversely affects the identity, strength, etc. of the drug. With this example, in this context, one could erroneously conclude that if qualification procedures show no safety concern, then the change has not adversely affected the identity, strength, quality, purity, or potency of the drug product.

Furthermore, many specifications and monographs for active ingredients, finished product release and stability testing include "total impurity" or "related compound" specifications. It is

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not uncommon to monitor a number of different, often unknown, impurities and/or degradants through these procedures. The appearance of a minor peak would not prompt characterization, nor should it require prior approval unless individual peak limits are exceeded, or the impurity is present at levels greater than 0.1%. For this reason, also, the example in the guidance, while possible, is not the best example and may lead to misinterpretation.

Line 252 Timeframe for Relocation of a Site: The draft language states "...but at some time it had been discontinued and now being restarted." A timeframe should be included in this draft. A two year timeframe is suggested.

Lines 285 – 287 Supplement - Changes Being Effected in 30 Days: The CBE 30 category is more restrictive than the current practice of site changing product manufacture immediately upon availability of site-specific stability data. It is our understanding that a firm is advised, but not required, to wait 30 days after submission of a CBE site-change supplement. The 30-day wait is particularly burdensome where a firm develops a new product at an R&D facility with the intent of submitting a CBE site-change supplement upon approval to launch immediately at an alternate site (after generation of 3-months accelerated data). If stability data are available and the product is validated at the alternate site, it is current practice to notify the district office when validation data is available for review, and ship product commensurate with district feedback.

Line 408 Major Changes (Prior Approval Supplement): The term "fundamental change" is vague and should be deleted. The examples which FDA presents are clear and provide sufficient detail to characterize this category of change.

Line 419 Major Changes (Prior Approval Supplement): The word "adversely" should be inserted between "may" and "effect".

Line 475 Moderate Changes (Supplements - Changes Being Effected): We believe that the CBE category can be extended to minor processing changes which may not qualify for annual report filings such as changes in tablet thickness and a change in the order of charging of ingredients (other than a solution dosage form).

Line 616 Composition of Packaging Materials: There is reference to composition of packaging materials which have not been previously approved by CDER. GPIA agrees with the position FDA is taking, however, we are concerned about the sponsor's access to information about packaging components (approved or unapproved) by CDER for particular dosage forms. Is this information readily available, and if so, from what source?

Lines 651 - 652 Container Size and Shape Change: GPIA is pleased to see that the changes which previously required prior approval are now being proposed as CBE supplements. In the case of container size/shape changes, it is our understanding that this change includes corresponding specification changes, such as neck size dimensions or wall thickness.

Line 661 -662 Compendial Packaging Changes: Currently, it is accepted practice that additions or changes in intermediate package sizes for solid oral dosage forms be added in annual

report updates. GPIA assumes that the example at 661 and 662 does not prohibit the current practice.

The Generic Pharmaceutical Industry Association appreciates this opportunity to provide our comments on the proposed rule.

Sincerely,

Alice E. Till, Ph.D.
President

CC: N. Sager, FDA (via mail and e-mail)
N. Tantillo, Chair GPIA CMC Taskforce

SPH31

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